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MERCK
Research Laboratories

Dockets Management Branch (HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: Docket No. 0[redacted]D-0361
International Conference on Harminization; Draft Guidance on ICH Q1D Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 Billion annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

As an innovative research and development company, Merck is affected by regulations which impact reporting requirements and therefore, we are interested in and qualified to comment on this draft guidance. The draft guidance on "ICH Q1D Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products" is intended to provide guidance on the application of reduced designs for stability studies conducted in accordance with the principles outline in ICH Q1A (R).

Merck supports the development of this draft guidance and to assist the further development, we are providing the following comments for your consideration.

Section 2.1 – General

Comment: This section discusses what should be done if the product appears less stable than expected. It allows reverting to a less reduced testing design but does not explain that this would need to be justified or how to go about justifying. Please clarify if the same principles relative to justification or reduced designs in the subsequent section are applicable in the case described here.

Section 2.3.2 - Design Considerations and Potential Risks
Line 121 – 123

Comment: This section states that if one of the extremes is no longer expected to be marketed that the study design can be maintained to support the bracketed intermediates. Further, the document states a commitment should be provided to carry out stability studies on the marketed extremes. Please clarify that this commitment is for post approval (per Q1A commitment batches) and needs only to include extremes marketed.

Section 2.4.2 – Design Considerations
Line 197 -199

Comment: Please clarify that if one of the factors (i.e. package, fill, strength) in the design develops an issue on stability unrelated to marketing needs, the matrix requires either reversion to full testing or justification of a reduced design. Please clarify how to justify a reduced design. (See comment section 2.1).

Section 2.4.4 Applicability and Degree of Reduction

Line 255 - 258

Comment: Please clarify what is meant by variability in this section. Consider further definition of the vague terms "very small" and "moderate" modifying variability and stability or remove the concepts. If the amount of variability or the stability of the product is adequate to define the stability profile via a full design study, then the reduced design should be compared to the power to detect difference relative to the full design. In this way the statistical justification relies on the reduction versus the full design and is independent of the product profile and the variability.

Line 260 -262

Comment: This section discusses statistical justification with respect to its power to detect differences. This is the first time that power or the justification is discussed. It is suggested that a brief explanatory note be added in Section 2.2 line 57: "In some reduced design situations, a statistical discussion of the design may be appropriate to provide justification of the reduced design versus full design's power to detect differences". Also provide a short list of references to provide additional guidance in basic statistical principles and reduced design development. One suggested reference: Nordbrock, E (1992), Statistical Comparison of Stability Study Designs, Journal of Biopharmaceutical Statistics, 2, 91-113.

We appreciate the opportunity to provide comments, which, from our perspective, will clarify some of the outstanding issues. We trust that these comments will be considered in further development of the proposed guidance.

Sincerely,

Michelle M. Kloss

for Dennis M. Erb. Ph.D.
Senior Director, Regulatory Liaison

q:In-line products/fr/guidance Q1D

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